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Can insulin resistance be predicted with vitamin B12, ferritin, vitamin D and demographic information using machine learning algorithms?

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Abstract

In this study, we aimed to investigate the relationship between insulin resistance and vitamin D, vitamin B12 and ferritin levels. Between January 2022 and October 2023, 322 patients (133 females, 189 males) between the ages of 3-16 years who were admitted to the Pediatrics outpatient clinics of İzmir Bakırçay University Çiğli Training and Research Hospital were included. Pediatric patients with no known chronic disease and measured vitamin B12, vitamin D, ferritin and HOMA-IR levels were retrospectively included in the study. Individuals with HOMA-IR<2.5 were considered as (normal) controls and those with HOMA-IR≥2.5 were considered as insulin resistant children. HOMA-IR groups were predicted with an accuracy rate of 0.80 with the Random Forest (RF) algorithm, one of the machine learning algorithms. In addition, the highest contribution of RF to the determination of HOMA-IR with the SHAP analyzer was found to be provided by age, followed by vitamin B12. The results of the study revealed that vitamin B12, vitamin D, ferritin level and age are important factors on insulin resistance. Early vitamin D, vitamin B12 and ferritin replacement is important for the control of metabolic diseases in the future.

Keywords: Vitamin B12, vitamin D, ferritin, insulin resistance

Introduction

Insulin is a polypeptide hormone produced by β cells in the islets of Langerhans of the pancreas that works in coordination with glucagon to regulate blood sugar levels. Insulin regulates glucose levels in the bloodstream and triggers glucose storage in the liver, muscles and adipose tissue, leading to overall weight gain [1]. Insulin resistance is a metabolic condition resulting from impaired response of insulin-related target tissues and organs to insulin stimulation. It can occur in all tissues with insulin receptors, but the target tissues mainly affected are the liver, skeletal muscle and adipose tissue [2].

Vitamin B12 is a complex organometallic compound consisting of a cobalt atom enclosed in a corine ring. It cannot be synthesized in the human body and must be obtained through diet [3]. Its source is animal foods. The most important functions of vitamin B12 are its role in erythropoiesis, cell division through DNA synthesis, myelinization of the nervous system through s-adenosyl methionine synthesis and epithelialization of the gastrointestinal tract [4]. Vitamin B12 deficiency in the population is between 3% and 40%. In children; 160-200 pg/mL for vitamin B12 is considered as deficiency and below 160 pg/mL is considered as severe deficiency [5]. Clinical pictures resulting from vitamin B12 deficiency are categorized in two main groups: hematologic and neuropsychiatric disorders. Symptoms may include weakness, fatigue, vomiting, diarrhea, constipation, anorexia, impaired neurocognitive functions, mental and motor retardation [6]. In vitamin B12 deficiency, it is known that neurological findings occur in 20-30% of patients without anemia clinic [3].

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Ferritin is critical for maintaining body iron balance and regulation and its dysregulation is a biomarker directly associated with iron deficiency (ID) and hemochromatosis. Ferritin is also associated with many metabolic diseases such as obesity [7].

Vitamin D regulates serum Ca levels and helps bone development. Adequate amounts are therefore vital for maintaining overall health. Vitamin D is synthesized either endogenously in the body or through diet and supplements. Vitamin D significantly promotes osteogenesis [8]. Vitamin D acts like a steroid hormone, controlling more than 200 genes and affecting many endocrine, metabolic, cardiovascular, autoimmune mechanisms [9].

Machine learning algorithms are engineering-based algorithms and are used in many topics such as age prediction, gender prediction, disease prediction in current studies in the field of health [10,11].

Although there are many studies on the link between vitamin D and insulin resistance in the world, there are few population-based studies on the link between vitamin B12 and ferritin and insulin resistance. In this study, we aimed to determine whether there is a link between age, vitamin B12, vitamin D and ferritin levels and insulin resistance and to guide early diagnosis and treatment.

Material and Methods

The study was performed by retrospectively examining the blood results of 133 female and 189 male children aged 3-16 years who were admitted to the Department of Pediatrics, İzmir Bakırçay University Çiğli Training and Research Hospital. The study was approved by the decision number 1300 of İzmir Bakırçay University Non-Interventional Local Ethics Committee. HOMA-IR, ferritin, vitamin D and vitamin B12 levels were screened in children. Individuals with HOMA-IR<2.5 were considered as (normal) controls and those with HOMA-IR≥2.5 were considered as insulin resistant children. Study groups were selected randomly and retrospectively among 2000 patients who applied to our hospital between 2022-2023. As an exclusion criterion, individuals' absence of HOMA-IR, ferritin, vitamin B12 and vitamin D blood findings was selected. Groups were selected based on HOMA-IR levels.

$$\text{HOMA-IR}=\frac{\text{Fasting Blood sugar x Fasting Insulin}}{405}$$

Equation 1. HOMA-IR formula

Design and implementation of machine learning algorithms

Machine learning algorithms were implemented using a personal computer with a Monster Abra model and Windows operating system. For algorithm modeling, Python 3.9 programming language and scikit-learn 1.1.1 framework were used. In modeling, 20% of the data was reserved as a test set. Machine learning algorithm models such as Decision Tree (DT), Random Forest (RF), Extra Tree Classifier (ETC), K-Nearest Neighbors (k-NN) Linear Discriminant Analysis (LDA) and Quadratic Discriminant Analysis (QDA) were preferred. The power of the models to reveal insulin resistance was obtained by the following formalization.

$$\text{Acc}=\frac{TP}{TP+FN+FP+TN}$$

$$\text{Sen}=\frac{TP}{TP+FN}$$

$$\text{Spe}=\frac{TN}{TN+FP}$$

$$F1=2\,\frac{\text{Precision}\times\text{Recall}}{\text{Precision}+\text{Recall}}$$

Equation 2. TP: true positive, FP: falsepositive, TN: true negative, FN: falsenegative

In addition, the tree structure of the DT algorithm and the SHAP analysis of the RF algorithm were included in the study.

Statistical analysis

Anderson Darling test was used as normality test. Median (minimum-maximum) values were used for descriptive statistics. Mann Whitney-U test was used for pairwise comparisons. The relationship between the parameters and the degree of relationship were evaluated using Spearman rho correlation test. In the analyses, $p<0.05$ was considered significant and Minitab 17 and SPSS 21 statistical programs were used.

Results

In this study in which 161 (109 males, 52 females) controls and 161 (80 males, 81 females) individuals with insulin resistance were analyzed, it was found that all of the data were not normally distributed. Descriptive statistics of the parameters and Mann Whitney U test results are given in Table 1. As a result of Mann Whitney U test, it was found that all parameters showed a significant difference in terms of HOMA-IR grouping ($p<0.05$).

The relationship between parameters and the degree of relationship were analyzed with the Spearman rho correlation test and between Ferritin and gender and age, between vitamin D and age, between vitamin B12 and age and vitamin D, and between HOMA-IR and age, gender, vitamin D and Vitamin B12. A significant relationship was found ($p<0.05$). Among these relationships, the one between HOMA-IR and age had a moderate relationship ($r = 0.674$), (Table 2).

As a result of machine learning algorithms analysis, the highest accuracy rate was found to be 0.80 with RF and DT algorithm (Table 3).

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Table 1. Descriptive statistics and pairwise comparison table

Parameters	HOMA-IR Group	Median (minimum-maximum)	p*
Age	Control	6 (3-16)	**0.000**
	Insulin resistance	13 (3-16)	
HOMA-IR	Control	0.8 (0.1-2.4)	**0.000**
	Insulin resistance	4.1 (2.6-10)	
Ferritin	Control	32 (5-226)	**0.024**
	Insulin resistance	41 (5-257)	
Vitamin D	Control	28 (10-59)	**0.000**
	Insulin resistance	20 (7.3-41)	
Vitamin B12	Control	518 (184-1166)	**0.000**
	Insulin resistance	377 (150-1149)	

*Mann Whitney U

Table 2. Spearman rho correlation table

Parameters	Gender	Age	Ferritin	Vitamin D	Vitamin B12
Age	0.080				
	0.152				
Ferritin	-0.145	0.218			
	0.009	**0.000**			
Vitamin D	-0.031	-0.340	-0.025		
	0.576	**0.000**	0.650		
Vitamin B12	-0.024	-0.410	-0.021	0.232	
	0.661	**0.000**	0.706	**0.000**	
HOMA-IR	0.126	0.674	0.107	-0.323	-0.357
	0.024	**0.000**	0.055	**0.000**	**0.000**

Table 3. Analysis of machine learning algorithms

Algorithms	Acc	Spe	Sen	F1
RF	0.80	0.80	0.80	0.80
DT	0.80	0.80	0.80	0.80
k-NN	0.77	0.78	0.77	0.77
ETC	0.74	0.74	0.74	0.74
LDA	0.74	0.74	0.74	0.74
QDA	0.71	0.71	0.71	0.71

RF: random forest, DT: decision tree, k-NN: k-nearest neighbors, ETC: extra tree classifier, LDA: linear discriminant analysis, QDA: quadratic discriminant analysis

As a result of the RF and DT algorithm, 27 of 33 individuals in the control group and 25 of 32 individuals in the insulin resistance group in the test set were correctly predicted (Figure 1).

The effect of parameters was investigated using the SHAP solver of the RF algorithm and it was found that the highest contribution was provided by age, followed by vitamin B12 (Figure 2).

The tree branching of the DT algorithm is shown in Figure 3. The biggest contribution is again the age parameter.

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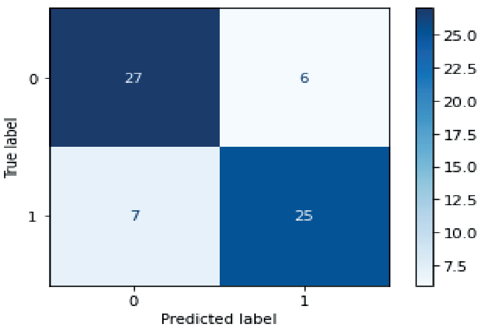

Figure 1. Confusion matrix table of RF and DT algorithm

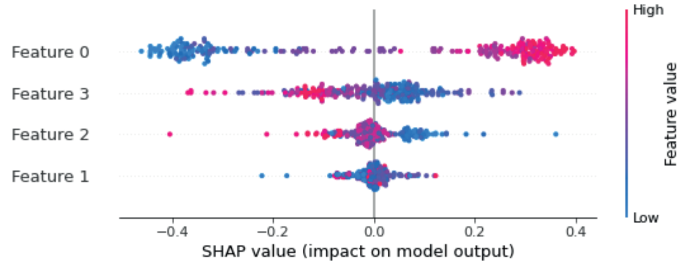

Figure 2. SHAP solver of the RF algorithm (Feature 0: age, 1: ferritin, 2: D vit, 3: B12 vit)

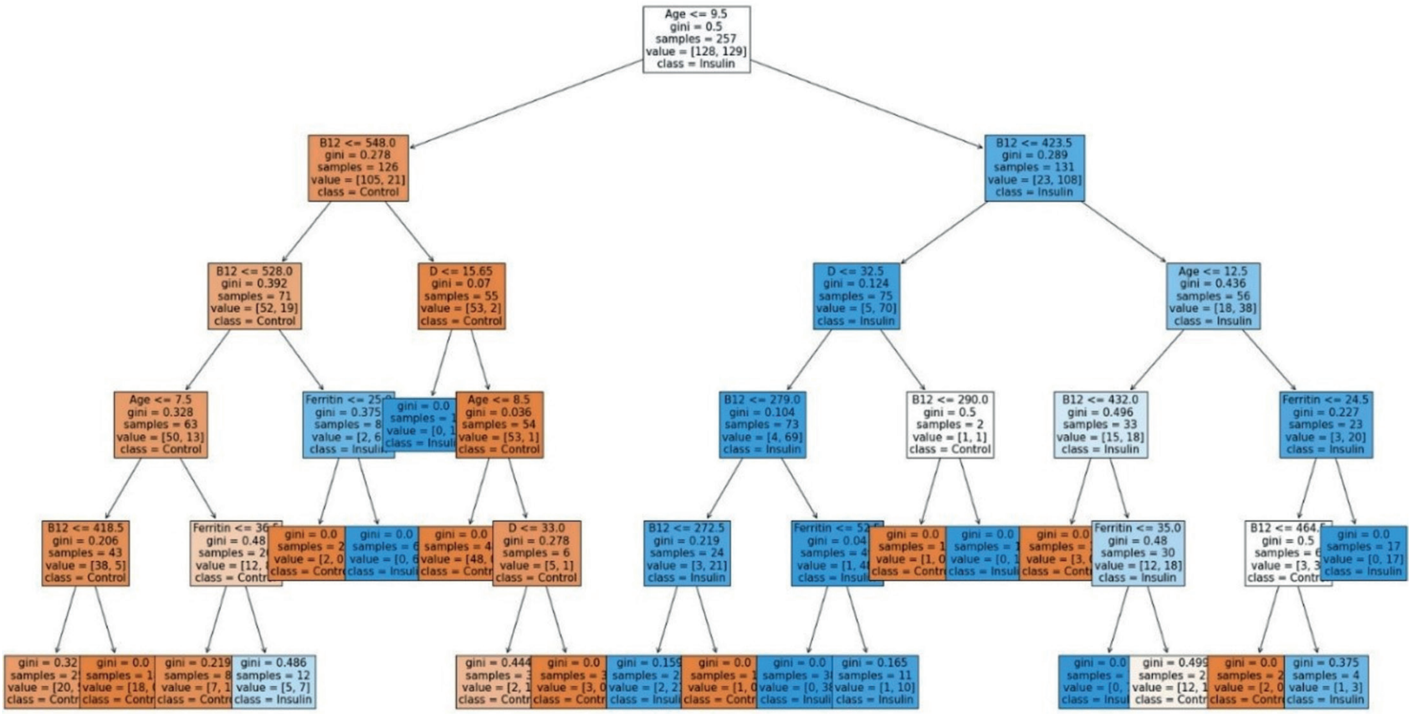

Figure 3. DT algorithm tree modeling

Discussion

In this study examining the relationship between HOMA-IR level and vitamin B12, vitamin D, ferritin and age, an accuracy of 0.80 was obtained with RF and DT algorithms from machine learning algorithms. In addition, it was determined that age, vitamin B12, vitamin D, ferritin and ferritin contributed to the determination of HOMA-IR level from high rate to low rate, respectively.

The increase in insulin resistance syndrome in recent years suggests that environmental factors are important [12]. In a systematic review study by Van der Aa et al. it was reported that the overall prevalence rates of insulin resistance ranged from 3.1% to 44% in children and adolescents and that it was more prevalent in females than in males due to the physiology of puberty [13]. Adolescence is thought to increase the risk of IR. Arslanian et al. showed that despite similar degrees of adiposity and glycemic status, the rate of insulin resistance was higher in obese adolescents than in obese adults [14]. Children and adolescents with obesity and insulin resistance are more prone to impaired glucose tolerance than those with obesity but without insulin resistance [15]. In our study, age was found to be the biggest factor in determining HOMA-IR with the SHAP analyzer of the RF algorithm.

Insulin resistance can lead to secondary metabolic disorders such as hyperglycemia, hyperuricemia, endothelial dysfunction and hypertension [16-20].

In a prospective study, 7791 patients aged 50-74 years were followed up for 8 years, 829 developed Type 2 Diabetes Mellitus; a significant and decreasing dose-response relationship was observed between Type 2 Diabetes Mellitus and vitamin D level in women with vitamin D ≤40 nmol/l, in contrast to men [21]. Sisman et al. 2019, an inverse correlation was found between vitamin D level and HOMA-IR [22]. In our study, a significant relationship was found between vitamin D and HOMA-IR level.

There is a complex relationship between ferritin and the metabolic syndrome, which remains unclear. Excess iron, which can manifest as high ferritin concentration, is associated with insulin resistance, which plays an important role in the development of metabolic syndrome. Iron is a transition metal that catalyzes radicals associated with oxidative stress/damage, resulting in the generation of reactive species [23]. There are several studies showing that high ferritin concentrations are associated with obesity. A US study showed that ferritin was associated with various body fat distribution and obesity indices [24]. It has shown that high ferritin levels are a consequence of chronic inflammatory reactions, as well as a result of increased iron stores [25]. A prospective cohort study in Korea showed that high serum ferritin levels may be a predictive factor for obesity in non-obese men over a 5-year follow-up period [7]. Studies in the literature show the relationship between ferritin and diabetes [26-28]. In 2014, a cross-sectional study of 8,235 participants in China reported that higher ferritin levels were associated with higher diabetes risks, higher HbA1c levels and higher HOMA-IR [29]. Liu et al. found significantly higher insulin resistance in adults with high ferritin levels in their study [30]. In this study, we found that ferritin level had a significant relationship between the control group and the insulin resistant group.

Limitations

Limitations of our study include the fact that factors affecting vitamin D levels such as climate, season, weight, ethnicity and lifestyle were not taken into account.

Conclusion

In conclusion; vitamin B12, vitamin D, ferritin and age are associated with insulin resistance. Maintaining optimal levels of vitamin D and vitamin B12 may protect against metabolic diseases and ensure healthier generations in the future. At the same time, ferritin level may be a parameter in the screening and follow-up of metabolic diseases and may increase our chances of predicting and following metabolic diseases with less cost.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

The study was approved by the decision number 1300 of İzmir Bakırçay University Non-Interventional Local Ethics Committee.

References

1. Rahman MS, Hossain KS, Das S, et al. Role of insulin in health and disease: an update. Int J Mol Sci. 2021;22:6403.
2. Alghamdi F, Guo M, Abdulkhalek S, et al. A novel insulin receptor-signaling platform and its link to insulin resistance and type 2 diabetes. Cell Signal. 2014;26:1355-68.
3. Çolak AA, Anıl M, Toprak B, et al. B12 vitamin level in children and its relationship with complete blood count parameters. İzmir Dr Behçet Uz Çocuk Hast Dergisi. 2012;2:75-9.
4. Black MM. Effects of vitamin B12 and folate deficiency on brain development in children. Food and nutrition bulletin. 2008;29:S126-31.
5. Garcia-Casal M, Osorio C, Landaeta M, et al. High prevalence of folic acid and vitamin B12 deficiencies in infants, children, adolescents and pregnant women in Venezuela. Eur J Clin Nutr. 2005;59:1064-70.
6. Carmel R, Watkins D, Rosenblatt DS. Megaloblastic anemias. In: Nathan and Oski's hematology and oncology of infancy and childhood. 8th edition. Elsevier Saunders, Philadelphia, 2015;20-308.
7. Park SK, Choi WJ, Oh C-M, et al. Association between serum ferritin levels and the incidence of obesity in Korean men: a prospective cohort study. Endocr J. 2014;61:215-24.
8. Gaur S, Nayak R. Underweight in low socioeconomic status preschool children with severe early childhood caries. J Indian Soc Pedod Prev Dent. 2011;29:305-9.
9. Öngen B, Kabaroğlu C, Parıldar Z. Biochemical and laboratory evaluation of vitamin D.Türk Klinik Biyokimya Derg. 2008;6:23-31.
10. Secgin Y, Oner Z, Turan MK, Oner S. Gender prediction with the parameters obtained from pelvis computed tomography images and machine learning algorithms. J Anat Soc India. 2022;71:204-9.
11. Senol D, Secgin Y, Duman BS, et al. Sex and age estimation with machine learning algorithms with parameters obtained from cone beam computed tomography images of maxillary first molar and canine teeth. Egyptian Journal of Forensic Sciences. 2023;13:27.
12. Al-Beltagi M, Bediwy AS, Saeed NK. Insulin-resistance in paediatric age: Its magnitude and implications. World J Diabetes. 2022;13:282-307.
13. Van der Aa M, Fazeli Farsani S, Knibbe C, et al. Population-based studies on the epidemiology of insulin resistance in children. J Diabetes Res. 2015;2015:362375.
14. Arslanian S, Kim JY, Nasr A, et al. Insulin sensitivity across the lifespan from obese adolescents to obese adults with impaired glucose tolerance: who is worse off?. Pediatr Diabetes. 2018;19:205-11.
15. Goldfine AB, Bouche C, Parker RA, et al. Insulin resistance is a poor predictor of type 2 diabetes in individuals with no family history of disease. Proc Natl Acad Sci U S A. 2003;100:2724-9. Erratum in: Proc Natl Acad Sci U S A. 2003;100:4970.
16. Seong J, Kang JY, Sun JS, Kim KW. Hypothalamic inflammation and obesity: a mechanistic review. Arch Pharm Res. 2019;42:383-92.
17. Brown JC, Harhay MO, Harhay MN. The value of anthropometric measures in nutrition and metabolism: comment on anthropometrically predicted visceral adipose tissue and blood-based biomarkers: a cross-sectional analysis. Nutr Metab Insights. 2019;12:1178638819831712.
18. Nolan CJ, Prentki M. Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: Time for a conceptual framework shift. Diab Vasc Dis Res. 2019;16:118-27.
19. Deacon CF. Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes. Front Endocrinol (Lausanne). 2019;10:80. Erratum in: Front Endocrinol (Lausanne). 2019;10:275.
20. Thomas DD, Corkey BE, Istfan NW, Apovian CM. Hyperinsulinemia: an early indicator of metabolic dysfunction. J Endocr Soc. 2019;3:1727-47.
21. Schöttker B, Herder C, Rothenbacher D, et al. Serum 25-hydroxyvitamin D levels and incident diabetes mellitus type 2: a competing risk analysis in a large population-based cohort of older adults. Eur J Epidemiol. 2013;28:267-75.
22. Sisman M, Erismis B, Mert M. Does vitamin D level affect insulin resistance?. Ortadoğu Tıp Derg. 2020;12:124-30.

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23. Arosio P, Levi S. Ferritin, iron homeostasis, and oxidative damage. Free Radic Biol Med. 2002;33:457-63.

24. Gillum R. Association of serum ferritin and indices of body fat distribution and obesity in Mexican American men—the Third National Health and Nutrition Examination Survey. Int J Obes Relat Metab Disord. 2001;25:639-45.

25. Esser N, Legrand-Poels S, Piette J, et al. NLRP3 inflammasome and visceral adipose tissue. Rev Med Liege. 2014;69:57-61.

26. Forouhi N, Harding A, Allison M, et al. Elevated serum ferritin levels predict new-onset type 2 diabetes: results from the EPIC-Norfolk prospective study. Diabetologia. 2007;50:949-56.

27. Kunutsor SK, Apekey TA, Walley J, Kain K. Ferritin levels and risk of type 2 diabetes mellitus: an updated systematic review and meta-analysis of prospective evidence. Diabetes Metab Res Rev. 2013;29:308-18.

28. Jehn ML, Guallar E, Clark JM, et al. A prospective study of plasma ferritin level and incident diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. 2007;165:1047-54.

29. Zhan Y, Tang Z, Yu J. Serum ferritin, diabetes, diabetes control, and insulin resistance. Acta Diabetol. 2014;51:991-8.

30. Liu B-w, Xuan X-m, Liu J-r, et al. The relationship between serum ferritin and insulin resistance in different glucose metabolism in nonobese Han adults. Int J Endocrinol. 2015;2015:642194.